UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

ARIAD PHARMACEUTICALS, INC., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, THE WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH, and THE PRESIDENT AND FELLOWS OF HARVARD COLLEGE	)	Civil Action No. 02 CV 11280 RWZ
Plaintiffs,	)	U.S. District Judge Rya W. Zobel
v.	)	
ELI LILLY AND COMPANY,	)	
Defendant.	)	

DEFENDANT ELI LILLY AND COMPANY'S MEMORANDUM IN SUPPORT OF ITS MOTION FOR SUMMARY JUDGMENT OF INVALIDITY UNDER 35 U.S.C. SECTION 102

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I. INTRODUCTION

Lilly's motion for summary judgment of invalidity raises a single issue of claim construction, one that is purely an issue of law for this Court to decide. There are no facts in dispute. The legal issue is simple. Plaintiffs, through their expert witnesses, contend that the asserted claims of U.S. Patent No. 6,410,516 ("the '516 patent")[1] are limited solely to methods that act directly on specific cells types containing NF-κB. Lilly, on the other hand, contends that this Court's prior *Markman* ruling makes it clear that the claims are not so limited. Plaintiffs are advancing a strained claim construction in conflict with this Court's prior ruling to avoid the invalidating prior art use of antibiotics. Plaintiffs have admitted that the use of antibiotics is an effective method for reducing lipopolysaccharides ("LPS"), which in turn acts to directly reduce NF-kB activity in those very same specific cell types. Thus, this motion presents a pure question of law in which the Plaintiffs are seeking to unilaterally revise the Court's claim construction so as to avoid this devastating and clearly invalidating prior art.

The claim construction issue for this Court boils down to this: Are the patent claims asserted against Lilly limited only to "methods" that ***directly*** intervene in the cell, or do they cover events outside of the cell that directly or indirectly "reduce NF-κB activity" within the cell?

Lilly contends that the '516 patent is invalid under 35 U.S.C. § 102(b) because "the invention [method of reducing NF-κB activity] was . . . described in a printed publication in this . . . country . . . more than one year prior to the date of the application

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[1] A copy of the '516 patent was previously submitted to the Court as Exhibit 1 to the Complaint, dated June 25, 2002. To avoid unduly burdening the couret with yet another copy, sections of the '516 patent quoted in the body of this memorandum refer to this previously submitted copy.

for patent in the United States." The 1970 Physician's Desk Reference ("*1970 PDR*" – Ex.1)[2] is such a printed publication. Plaintiffs do not, and cannot, dispute any of the material facts supporting Lilly's position, as expressed by its expert Dr. Manolagas, regarding the action of antibiotics when administered as taught in the *1970 PDR*. Specifically, plaintiffs cannot dispute that:

1) the *1970 PDR* is a written publication that was publicly available more than one year from the earliest filing date of the '516 patent;

2) a gram-negative bacterial infection will produce LPS;

3) LPS will induce an increase in NF-κB activity within cells;

4) antibiotic administration to treat the infection as taught by the *1970 PDR*, and as used in patients for more than three decades before the discovery of NF-κB, will necessarily reduce LPS; and

5) reducing LPS will in turn necessarily reduce NF-κB activity in the cells.

(Exs. 2 & 3 – Manolagas Expert Report & Manolagas Declaration).

Plaintiffs incorrectly argue that the language of the asserted claims of the '516 patent requires that the administered antibiotic must act directly on the cells with raised levels of NF-κB as opposed to acting on the bacteria that is causing the production of the LPS. As explained below, there is no such limitation in the claims or in this Court's previously determined claim construction. Lilly contends that administering an antibiotic accomplishes the claimed method of reducing the NF-κB activity in the cells, in that, ***as a matter of law***, the claims do not require direct intervention within the cell.

In fact, because the asserted claims use the open ended language "comprising" in reference to "reducing NF-κB activity" within the cell, the claimed "methods" can

[2] References to "Robins Decl., Ex. _____" are to exhibits to the Declaration of Lawrence R. Robins in Support of Eli Lilly's Motion for Summary Judgment of Invalidity Under 35 U.S. C. Section 102.

include many un-recited steps, upstream or downstream of the cell itself as long as NF-κB activity is in fact ultimately reduced within the cell. Specifically, if a human patient develops a gram-negative bacterial infection, LPS is released by the gram-negative bacteria, which, in turn contacts cells in the patient's body and induces an increase in the activity level of NF-κB within the cells, resulting in the expression of LPS-induced cytokines. Partially or wholly blocking this source of LPS, by use of a "method," for example, of administering antibiotics to that patient that ultimately inhibit or kill the gram-negative bacteria would reduce the amount of LPS in contact with the induced cells, thereby necessarily reducing NF-κB activity within the cell and the expression of LPS-induced cytokines. (Exs. 2 & 3 - Manolagas Expert Report and Manolagas Declaration).

Plaintiffs themselves have taken the position that such indirect effects are within the scope of the claims of the '516 patent. In fact, one of plaintiffs' experts, Dr. Boyce, has taken the position that compounds that interact outside of the cell will reduce NF-κB activity within the cell. Dr. Boyce discussed the action of a natural compound, osteoprotegrin, which acts to reduce binding of an NF-κB inducer, RANKL to a receptor on osteoclast precursor cells known as RANK. (Ex. 4 – Boyce Report, pg. 9). According to Dr. Boyce, by stopping the binding of this NF-κB activator to the surface of cells when it is upregulated, ostroprotegrin reduces the induction of NF-κB, thereby reducing NF-κB activity in the osteoclast precursor cells and reducing NF-κB-mediated effects.

II. UNDISPUTED FACTS

A. NF-KB Activity

Transcription factor NF-κB refers to a small group of cellular proteins that function inside a living cell. The NF-κB proteins are involved in a complex biological signaling system that regulates gene expression by turning gene transcription on and off. NF-κB proteins are inducible factors which, when activated, respond to a wide variety of external influences. Prior to being activated, NF-κB is bound to a protein known as IκB in the cell cytosol or cytoplasm. Upon activation from stimulus outside the cell, NF-κB is released from IκB, so that it may move into the nucleus of the cell. Once inside the nucleus, NF-κB binds to certain sites known as "recognition sites" on DNA. Once bound, NF-κB will "turn on" transcription of certain genes, causing proteins to be expressed by the cell machinery. Thus, modulation of NF-κB activity in turn results in the stimulation or inhibition of transcription of certain genes, thereby affecting corresponding protein production. These naturally-occurring mechanisms are generally referred to collectively as the "NF-κB pathway." NF-κB and the NF-κB pathway have played this role as mediator of cell signaling in humans for as long as humankind has existed. It even predates the evolution of humans from other mammals more than 30 million years ago.[3]

[3] As noted by Dr. Sharp, one of the co-inventors of the '516 patent, indicated that NF-κB activity existed before he and the other inventors studied it and that it has existed for at least 30 million years. (Ex. 5 - Sharp dep., pp. 221-222).

B. Asserted Claims of the '516 Patent

The claims asserted against Lilly by Plaintiffs substantially overlap with each other.[4] As shown below, all of the asserted claims are (1) method/process claims calling for (2) the same single functional step of "reducing NF-κB activity" to achieve various claimed results:

Claims Asserted Against EVISTA®	Claims Asserted Against XIGRIS®
6. **A method** for diminishing induced NF-κB-mediated intracellular signaling comprising **reducing NF-κB activity** in cells such that NF-κB-mediated intracellular signaling is diminished. [Asserted claims 69 and 71 depend from this claim]	14. **A method** for reducing bacterial lipopolysaccharide-induced expression of cytokines in mammalian cells, which method comprises **reducing NF-κB activity** in the cells so as to reduce bacterial lipopolysaccharide-induced expression of said cytokines in the cells. [Asserted claims 144-146 depend from this claim]
7. **A method** for modifying effects of external influences on a eukaryotic cell, which external influences induce NF-κB-mediated intracellular signaling, the method comprising **altering NF-κB activity in the cells** such that NF-κB- mediated effects of external influences are modified. [Asserted claims 80 and 84 depend from this claim]	144. **The method** of claim 14 wherein reducing NF-κB activity comprises reducing binding of NF-κB to NF-κB recognition sites on genes which are transcriptionally regulated by NF-κB.
8. **The method** of claim 7, wherein **NF-κB activity in the cell is reduced**. [Asserted claims 80 and 84 depend from this claim]	145. **The method** of claim 14, carried out on human cells.
9. **A method** for reducing, in eukaryotic cells the level of expression of genes which are activated by extracellular influences which induce NF-κB-mediated intracellular signaling, the method comprising **reducing NF-κB activity** in the cells such that	146. **The method** of claim 14 or 145, carried out on immune cells.

[4] Although the '516 patent contains 203 claims related to this naturally occurring NF-κB pathway, only 10 of these claims are currently being asserted against Lilly. Therefore, these asserted claims are the only claims addressed specifically in this motion for purposes of summary judgment.

expression of said genes is reduced. [Asserted claims 93-95 depend from this claim]

69. **The method** of claim 6 wherein reducing NF-κB activity comprises reducing binding of NF-κB to NF-κB recognition sites on genes which are transcriptionally regulated by NF-κB.

71. **The method** of claim 6, carried out on human cells.

80. **The method** of claim 8 wherein reducing binding of NF-κB to NF-κB recognition sites on genes which are transcriptionally regulated by NF-κB.

84. **The method** of claim 8, carried out on human cells.

93. **The method** of claim 9 wherein reducing NF-κB activity comprises reducing binding of NF-κB to NF-κB recognition sites on genes which are transcriptionally regulated by NF-κB.

94. **The method** of claim 9, carried out on mammalian cells.

95. **The method** of claim 9, carried out on human cells.

Each of these asserted claims is generally directed to methods of causing some type of effect in a cell by reducing NF-κB activity in that cell. Thus, for example the claims call for reducing NF-κB such that induced NF-κB-mediated intracellular signaling is diminished (Claim 6); or, such that NF-κB-mediated effects of external influences on a eukaryotic cell, which external influences induce NF-κB-mediated intracellular signaling, are modified or reduced (claims 7 and 8); or, such that, in eukaryotic cells, expression of

genes which are activated by extracellular influences which induce NF-κB-mediated intracellular signaling is reduced (claim 9); or, such that, in mammalian cells, bacterial lipopolysaccharide-induced expression of cytokines like TNF-α is reduced (claims 14 and 15).

These effects clauses in the claims are not mutually exclusive. For example, where bacterial lipopolysaccharide ('LPS")-induced expression of cytokines, like TNF-α, in mammalian cells is regulated by NF-κB, this constitutes expression of a gene or genes whose transcription is regulated by NF-κB. Thus, if bacterial LPS-induced expression of cytokines, like TNF-α, in mammalian cells is reduced by reducing NF-κB activity (as called for by claims 14 and 15), this would also inhibit expression of a gene or genes whose transcription is regulated by NF-κB. Moreover, some of the claims require that NF-κB activity be reduced in certain ways, such as by reducing binding of NF-κB to NF-κB recognition sites on genes that are transcriptionally regulated by NF-κB (e.g., claim 69).

Again, these added limitations as to how NF-κB activity is to be reduced are not mutually exclusive. Something that works upstream to reduce NF-κB activity by, for example, inhibiting the modification or degradation of an IκB protein will decrease the level of NF-κB not bound in an NF-κB:IκB complex. The unmodified or undegraded IκB protein will bind to NF-κB to form a complex, leaving less unbound NF-κB, and thus reducing NF-κB activity. Similarly, because the unmodified or undegraded IκB protein complexes with NF-κB, it will inhibit the translocation of NF-κB into the nucleus of cells. Finally, because there is less unbound NF-κB to translocate into the nucleus, the

unmodified or undegraded IκB protein will reduce binding of NF-κB to NF-κB recognition sites on genes which are transcriptionally regulated by NF-κB (as called for by claim 69).

C. Antibiotics Administration for Infections

Antibiotics, including erythromycin, gentamicin and tetracycline, have been administered for decades before the discovery of NF-κB to treat gram-negative bacterial infections. (Ex.3). The 1970 Physicians' Desk Reference ("*1970 PDR*"), for example, teaches the administration of erythromycin, gentamicin and tetracycline for such gram-negative bacterial infections as *H. pertussis*, *E. coli,* and *Shigella*. (Ex. 1, pgs. 1379, 1167 and 1309). In particular, gram-negative bacteria, such as *E. coli, Salmonella, Pseudomonas aeruginosa, Shigella*, *V. parvulla*, and *H. pertussis*, produce a compound known as lipopolysaccharide, or LPS. When LPS comes into contact with cells in a system, such as the human body, it is now known to induce NF-κB activity and, in turn, increase the production of cytokines that are regulated by NF-κB activity. (Ex. 3). Administering antibiotics to a patient to treat the bacterial infection, as clearly taught in *1970 PDR* to resolve gram-negative infections, would thus ultimately and necessarily reduce NF-κB activity and thereby reduce the expression of LPS-induced (and NF-κB-regulated) cytokines. (Ex. 3).

LPS, when produced by gram-negative bacteria, activates NF-κB, which translocates to the nucleus and binds to the NF-κB recognition sites on genes that are regulated at least in part by NF-κB. (see the '516 patent - col. 2, lines 54-57 -"Release of active NF-κB from the IκB-NF-κB complex has been shown to result from stimulation of cells by a variety of agents, such as bacterial lipopolysaccharide . . . ."). Cytokines,

whose genes are now known to be regulated by NF-κB (at least in part), include TNF-α, IL-2, IL-6, IL-8 and IL-10. (Exs. 6, 7& 8 - Galdiero, *et al.*, *Porins From* Salmonella enterica *Serovar Typhimurium Induce TNF-α, IL-6 and IL-8 Release By CD14-Independent and CD11a/CD18-Dependent Mechanisms*, MICROBIOLOGY 147:2697-2704 (2001) ("*Galdiero*"); Yang, *et al.*, *Toll-Like Receptor-2 Mediates Lipopolysaccharide-Induced Cellular Signaling,* NATURE 395:284–288 (September1998); and Mori, *et al.*, *Activation Of the Interleukin-10 Gene In the Human T Lymphoma Line HuT 78: Identification and Characterization Of NF-kB Binding Sites In the Regulatory Region Of The Interleukin-10 Gene*. EUR. J. HAEMATOL. 59:162-170 (1997).

When antibiotics are used to treat gram-negative bacterial infections they interfere with the normal function of the bacteria and ultimately reduce bacterial production of LPS. When a gram-negative bacterial infection is resolved, bacterial production of LPS is eliminated. By reducing the amount of LPS present in a system, the antibiotics necessarily reduce NF-κB activity in surrounding cells and the concomitant expression of NF-κB-regulated and bacterial LPS-induced cytokines in the cells. (Ex. 3). Indeed, *Galdiero* notes that, "The lowest concentration of LPS able to induce cytokine release was 10 ng ml^{-1} . . . ." (Ex. 6). Reducing LPS to levels below 1 μg/ml with any antibiotic – such as by resolving the underlying infection – would completely eliminate NF-κB-mediated cytokine production. (Ex. 3). Therefore, by partially or wholly blocking LPS that reaches the cell, or reducing it below the level required to induce cytokine production, the administration of these antibiotics as taught in the *1970 PDR* would necessarily reduce NF-κB activity in cells in a system, such as the human body, and thereby reduce the expression of cytokines, such as TNF-α, IL-6, IL-8 and IL-10. *Id.*

III. THE STANDARD FOR SUMMARY JUDGMENT

"Summary judgment is as appropriate in a patent case as any other where there is no genuine issue of material fact and where the movant is entitled to judgment as a matter of law." *C.R. Bard, Inc. v. Cordis Corp.*, No. 89-0606-Z, 1990 U.S. Dist. LEXIS 18460, at *3 (D. Mass. Aug. 30, 1990). A genuine issue of material fact exists only when "the evidence is such that a reasonable jury could return a verdict for the nonmoving party." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986).

A patent is invalid if "the invention was patented or described in a printed publication . . . more that one year prior to the date of the application for patent in the United States. . ." 35 U.S.C. § 102(b) (2000). Whether a document is a printed publication bar is a question of law. *In re Klopfenstein*, 380 F.3d 1345, 1348 (Fed. Cir. 2004); *Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1330 (Fed. Cir. 2004). The "printed publication" bar is grounded on the principle that once an invention is in the public domain, it is no longer patentable by anyone. *In re Klopfenstein*, 380 at 1349; *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1379-80 (Fed. Cir. 2001).

A movant is entitled to summary judgment of patent invalidity based on anticipation where (1) there are no material facts in dispute relating to the assertion of anticipation; and (2) the movant presents clear and convincing evidence that the prior printed publication anticipates the claimed subject matter in issue. *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1378 (Fed. Cir. 2001). A single prior art reference anticipates a patent claim if it expressly or inherently describes each and every limitation set forth in the patent claim. *Trintec Ind., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295

(Fed.Cir. 2002) (citing *Verdegaal Bros., Inc. v. Union Oil Co.,* 814 F.2d 628, 631 (Fed.Cir.1987)). "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed functions, it anticipates." *Atlas Powder Co. v. IRECO, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999). The *Atlas* Court further stated that,

> the discovery of a previously unappreciated property of a prior art composition *or of a scientific explanation for the prior art's functioning*, does not render the old composition patentably new to the discoverer." An inherent structure, composition or function is not necessarily known. * * * Insufficient prior understanding of the inherent properties of a known composition does not defeat a finding of anticipation.
>
> . . .
>
> The public remains free to make, use or sell prior art compositions or processes, *regardless of whether or not they understand...the underlying scientific principles which allow them to operate.*

Id. at 1348 (emphasis added).

The Manual of Patent Examining Procedure ("MPEP") provides that the transitional phrases "comprising", "consisting essentially of" and "consisting of" define the scope of a claim with respect to what unrecited additional components or steps, if any, are excluded from the scope of the claim. MPEP, 8th ed., rev. 1 § 2111.03 (2003); *See Ethicon, Inc. v. Quigg,* 849 F.2d 1422, 1425 (Fed.Cir.1988); *In re Kaghan,* 55 C.C.P.A. 844, 387 F.2d 398, 401 (1967) ("[A]n applicant should be entitled to rely not only on the statutes and Rules of Practice but also on the provisions of the MPEP in the prosecution of his patent application."). The MPEP specifically provides that "[t]he transitional term 'comprising'. . . is synonymous with 'including,' 'containing,' or 'characterized by,' [and] is open-ended and does not exclude additional, unrecited elements or method steps." MPEP at § 2111.03 (2003); *see, e.g., Genentech, Inc. v. Chiron Corp.,* 112 F.3d 495, 501 (Fed.Cir.1997) (" 'Comprising' is a term of art used in

claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim."). Thus, the term "comprising" is an open ended term that does not exclude additional, unnamed steps in a method claim.

IV. THE '516 PATENT IS INVALID UNDER 35 U.S.C. §102 BECAUSE IT COVERS ANTIBIOTIC TREATMENT METHODS DESCRIBED IN A 1970 PRINTED PUBLICATION

A. Questions of Law for this Court to Answer

The questions presented in this summary judgment motion are not fact based, they are questions of law. If the Court answers the following questions in the affirmative, then summary judgment of invalidity is necessary and proper, and this litigation should end.

1) Do the asserted claims of the '516 patent cover methods that ultimately cause a reduction in NF-κB activity in cells, regardless of whether the methods acts directly or indirectly on such cells?

2) Is the *1970 PDR* reference, teaching the administration of antibiotics for bacterial infections, a printed publication publicly available before January 9, 1986, the earliest possible filing date of the '516 patent?[5]

B. The Claims of the '516 Patent Are ***Not*** Limited to Only Methods That Directly Effect Cells

This Court has construed the claim terms that the parties indicated were in dispute and nowhere in that construction is there any limitation that an accused method must act directly on cells that contain NF-κB. (Ex. 9 – March 3, 2004 Order). Plaintiffs had the opportunity to try and convince the Court to narrowly construe the claims, but they chose not to. As the claim chart above shows, each one of the asserted claims uses the open-

[5] In fact, the U.S. Patent Office has recently held that the claims of the '516 patent are only entitled to an effective filing date of November 13, 1991 (Ex. 10 – December 12, 2005 Patent Office Order granting a request for reexamination.

ended "comprising" language and thus, "other elements may be added [to a claimed method] and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.,* 112 F.3d 495, 501 (Fed.Cir.1997). The only limitation to a "method" that is covered by the claims is that the end result reduces or alters the NF-κB activity in cells. There is absolutely no limitation in the claims whereby the "method" must act directly on the cells. In other words, the claims do not require that the chain of events leading to a reduction in NF-κB activity begin or originate from any particular location. Using the plain meaning of the claims and Federal Circuit precedent for construing transitional language leads to the conclusion that the claimed "method" can act directly ***or*** indirectly on cells containing NF-κB. The only limitation required by the asserted claims is that the "method" must ultimately cause NF-κB to be reduced or altered. Claim 71 is representative;

> 71. A method for diminishing induced NF-κB-mediated intracellular signaling comprising reducing NF-κB activity in human cells such that NF-κB-mediated intracellular signaling is diminished.

(see claims of the '516 patent). Nothing in this claim requires that the "method" for "diminishing induced NF-κB mediated intercellular signaling" must act directly on the cell itself. Likewise, nothing in this Court's previously issued claim construction Order of March 3, 2004 requires such a direct effect. (Ex. 9).

Most telling is that Plaintiffs themselves have taken the position that such ***indirect*** effects are within the scope of the claims of the '516 patent. In fact, one of plaintiffs' experts, Dr. Boyce, has stated that compounds that interact outside of the cell will reduce NF-κB activity within the cell. Dr. Boyce discussed the action of a natural compound, osteoprotegrin, which acts to reduce binding of an NF-κB inducer, RANKL to a receptor

on osteoclast precursor cells known as RANK. (Ex. 4 – Boyce Report, pg. 9). As indicated by Dr. Boyce, by stopping the binding of this NF-κB inducer to the surface of cells, osteoprotegrin reduces the induction of NF-κB, thereby reducing NF-κB activity in the osteoclast precursor cells and reducing NF-κB-mediated effects. If osteoprotegrin can reduce NF-κB activity within the meaning of the claims by acting outside cells, so too can antibiotics.

C. The Use of Antibiotics to Treat Infections as Taught in the *1970 PDR* Anticipates and Invalidates Each Asserted Claim of the '5116 Patent

Lilly's expert, Dr. Manolagas, succinctly sets forth the undisputed facts in his declaration that he submitted to the United States Patent and Trademark Office in support of a request for reexamination of the '516 patent[6], in which he states that;

1) the *1970 PDR* is a written publication that was publicly available at least 10 years before the discovery of NF-κB by the inventors of the '516 patent. The *1970 PDR* teaches administering antibiotics, including erythromycin, gentamicin and tetracycline, to treat gram-negative bacterial infections as *H. pertussis*, *E. coli,* and *Shigella*;

2) gram-negative bacteria in a system (human or otherwise) will produce lipopolysaccharide ("LPS");

3) when LPS comes into contact with cells in a system it will induce an increase in NF-κB activity within those cells. The '516 patent, in fact, repeatedly states that LPS induces NF-κB activity in cells (see the '516 patent - col. 2, lines 54-57 ("Release of active NF-κB from the IκB-NF-κB complex has been shown to result from stimulation of cells by a variety of agents, such as bacterial lipopolysaccharide . . . ."); col. 68, lines 30-55; col. 69, lines 40-41; 70, lines 18-31; 70, lines 59-62; and col. 72, lines 24-29);

4) use of antibiotics to treat gram-negative infections in a system, as taught by the *1970 PDR*, will resolve the infection, reducing and ultimately eliminating the bacterial production of LPS in the system; and

[6] Lilly's request for reexamination resulted in an Order by the Patent Office granting reexamination of the '516 patent. (Ex. 11). Also, a second party independently requested reexamination of the '516 patent and the Patent Office recently granted that request on December 12, 2005. (Ex.10).

5) reducing LPS in the system will necessarily reduce NF-κB activity and the concomitant expression of NF-κB-regulated and bacterial LPS-induced cytokines in cells within the system.

(Ex. 3, pgs. 17-19).

Significantly, Plaintiffs' rebuttal expert witnesses did not, and could not, dispute any of Dr. Manolagas' factual conclusions. (Prescott rebuttal - Ex. 12, pgs. 56-57; Dr. Ravetch rebuttal – Ex. 13, pgs. 33-34). As such, Plaintiffs have admitted all the material facts necessary to resolve this motion in Lilly's favor. In fact, the only challenge to Dr. Manolagas' description of how antibiotics affect NF-κB was one of claim construction, which is a question of law that only this Court can resolve:

> These claims require that the method alter the cells' response, not alter the substance to which the cell responds.
> . . .
> Since administration of antibiotics alters the function of bacteria, and not the cells specified by the claims, administration of antibiotics does not anticipate the claimed method.

(Prescott rebuttal – Ex. 12, pgs. 56-57). In essence, Plaintiffs' argument is that the asserted claims require that the "method," in this case the use of antibiotics, must act directly on the cells containing NF-κB. In fact, as explained above, there is no such requirement in any of the asserted claims. Plaintiffs do not even attempt to refute that reducing the amount of LPS that comes into contact with the cell will in fact reduce NF-κB activity within the cell, and reduce LPS-induced expression of cytokines, as called for by, *inter alia,* claim 14.

Since the asserted claims of the '516 patent read on both direct and indirect methods of reducing NF-κB activity, the administration of antibiotics to treat infections in 1970, as described in the *1970 PDR*, is invalidating prior art.

V. CONCLUSION

The asserted claims of the '516 patent encompass the use of antibiotics to treat gram-negative infections, a treatment that has been used by physicians for at least 15 years before the earliest filing date of the '516 patent. The 1970 Physicians' Desk Reference fully describes the use of antibiotics and constitutes an invalidating published prior art reference. Therefore, Lilly respectfully requests that summary judgment of invalidity under U.S.C. §102(b) be granted.

Date: December 23, 2005

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